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The Perils of Inhibiting Deficient Factors

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Essentials

- Anticoagulation in patients with factor X deficiency is an evidence-poor area.
- A patient with factor X deficiency was anticoagulated with warfarin followed by rivaroxaban.
- Warfarin may be a safer anticoagulant option than rivaroxaban in hereditary factor X deficiency.
- A baseline coagulation screen should be performed prior to commencement of anticoagulation.

Abstract

We report a case of a previously undiagnosed factor X deficiency in an 83-year old man, who had no previous bleeding history despite multiple haemostatic challenges. He was anticoagulated with warfarin for atrial fibrillation (AF) without bleeding complications; however, major haemorrhage occurred soon after a switch to rivaroxaban.

Case Description

An 83-year old man presented to the anticoagulation clinic requesting a switch from warfarin to rivaroxaban, due to a poor time in therapeutic range (TTR) and the inconvenience of INR monitoring. He had been on warfarin for 15 years for stroke prevention in the context of AF. His CHA_2DS_2 VASc score was 3 (age >75 years and history of ischaemic heart disease) equating to a 3.2% annual stroke risk [1]. His target INR range was 2.0-3.0 with a TTR of only 44%, spending approximately 20% of the time supra-therapeutic. He required a warfarin dose of 1-2mg daily with INR monitoring every 2-3 weeks. His previous medical history included laryngeal carcinoma, coeliac disease, hypercholesterolemia, coronary artery bypass grafting and chronic

kidney disease. The estimated creatinine clearance (Cockcroft-Gault) was 50 ml/min. He had no family or personal bleeding history either prior to, or whilst on, warfarin.

Warfarin was stopped, and when the INR had fallen below 2.5 he was switched to rivaroxaban 20mg once daily, and routinely reviewed after 3 weeks. The 6-hour rivaroxaban level, was 365ng/ml (expected range at this time point: 123-318ng/ml) [2]. Rivaroxaban concentrations were determined by anti-Xa activity using the STA anti-Xa assay (Diagnostica Stago, Asnieres-sur-Seine, France). Six weeks following commencement of rivaroxaban he presented to the Emergency Department with continuous bleeding from the mouth and gums, which had lasted for over 14 hours. Rivaroxaban was stopped, and he was prescribed tranexamic acid mouthwash. Admission bloods revealed haemoglobin 121 g/L (7.51 mmol/L), platelets 195 x 10^9/L, creatinine 110 umol/L, urea 8.5 mmol/L, INR 5.53 and APTT ratio 1.73. The following day, the haemoglobin had fallen to 96 g/L (5.95 mmol/L), indicating a major haemorrhage according to the International Society on Thrombosis and Haemostasis (ISTH) definition [3]. At this point, INR was 2.41 and the APTR had normalized. A rivaroxaban level taken at 30 hours post dose was reported as 119 ng/ml. He was discharged home the following day without anticoagulation. Two weeks later the INR was still prolonged at 1.54 and a 50:50 mixing study completely corrected, raising the suspicion of an underlying coagulation factor deficiency. The coagulation factor X level was measured at 34 u/dl (50-150 u/dl) consistent with mild factor X deficiency, which at this level is unlikely to cause a bleeding phenotype. Mutation analysis confirmed heterozygosity for a c.400G>A substitution in exon 5 of the factor X gene.

Factor X deficiency is an autosomal recessive bleeding disorder with a prevalence of 1:1 000 000 [4]. It usually presents with mucocutaneous bleeding, particularly heavy menstrual bleeding in women [5]. His treatment options were reviewed in light of the diagnosis of mild factor X deficiency. It was decided, based on his previous experience of having taken warfarin

safely for 15 years, to recommence this. An alternative option would have been to use the direct thrombin inhibitor dabigatran. In over a year of subsequent follow up, there have not been any further bleeding problems reported. Factor X level measured whilst on warfarin was 12 u/dl.

There are a number of potential reasons why bleeding occurred on rivaroxaban but not on warfarin. The patient was in effect overdosed with rivaroxaban as the pre-existing factor X was already low. In contrast, the residual factor X activity (12 u/dl) on warfarin is likely to be sufficient to maintain adequate haemostasis and confer protection against bleeding. In addition, anticoagulation with warfarin results in a consistent reduction in thrombin generation over time, in contrast to the pharmacokinetic peaks and troughs in anticoagulant effect which is seen with relatively short-acting once-daily direct oral anticoagulants (DOACs) [6].

Although DOACs have been shown to be associated with a lesser risk of intracranial haemorrhage than warfarin, mucocutaneous bleeding (for example heavy menstrual bleeding) is seen more frequently than with warfarin [7]. The presentation of our patient with oral bleeding was perhaps unsurprising, given the combination of anticoagulant and underlying condition.

Bleeding disorders like factor X deficiency are rare but atrial fibrillation is highly prevalent in the elderly population and the issue of anticoagulation in such patients will occasionally arise and remains a poorly understood therapeutic area. Guidelines exist for anticoagulating haemophiliacs with factor VIII and IX deficiency and AF but such guidance does not exist in patients with rarer inherited bleeding disorders. Review of the notes did not reveal a baseline coagulation screen prior to the first initiation on warfarin 15 years previously. This might have revealed the diagnosis of factor X deficiency earlier and enabled a more 'informed' view of

anticoagulation options. Due to the lack of data regarding anticoagulation in such scenarios it might well have deterred usage of anticoagulation per se. There are several considerations to take in account when anticoagulating patients with rare bleeding disorders, including bleeding history, indication for anticoagulation therapy, intended duration of therapy and characteristics of the individual anticoagulant drug options [8]. Further, we are able to monitor DOAC levels if required, but the implications of such levels and the relation to thrombotic and bleeding risk remain incompletely understood [9].

Authorship

Z. Sayar and V. Speed wrote the manuscript. R. Arya provided regular follow up and identification of the patient. J. P. Patel, R. K. Patel and R. Arya reviewed the manuscript for accuracy and interpretation.

Disclosure of Conflict of Interests

R. Arya reports Investigator-initiated research funding from Bayer Healthcare and Covidien and honoraria from Bayer Healthcare, Boehringer-Ingelheim, Pfizer and Sanofi., outside the submitted work. V. Speed reports honoraria from Bayer Healthcare, outside the submitted work.

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